35 U.S.C. §112 Rejection of the Claims

The final Office Action mailed June 18, 2002 and the Advisory Action dated October 21, 2002 maintained that the pending claims where indefinite under 35 U.S.C. § 112, second paragraph for reciting "comprising essentially of" and "lacks a loxP sequence." All previously pending claims have been cancelled with the exception of claim 22, and claim 22 has been amended to no longer recite "comprising essentially of" and "lacks a loxP sequence," thereby rendering this rejection moot. Applicant therefore requests that the Examiner withdraw the rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. §103 Rejection of the Claims

1. Aoki et al. in view of Chinnadurai et al.

Claims 4, 5, 10, 11 and 13-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* (Molecular Medicine, 5: 224-231 (1999)) and Chinnadurai *et al.* (Journal of Virology, 32(2): 623-628 (1979)). All of these claims have been cancelled or amended, thereby rendering this rejection moot. Insofar as the Examiner may apply this rejection over the pending claims, Applicant presents the following statements.

In order to establish a *prima facie* cases of obviousness, all three of the following factors must be met. First, the references themselves must teach or suggest all the limitations of the claims. Second, there must be a reasonable expectation of success at the time the invention was made. Third, the prior art must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference, or to combine references.

Chinnadurai *et al.* teach growing Ad2 and Ad5 viral particles, protein digesting the particles, isolating the full-length genomes from the viral particles, digesting Ad2 DNA with *Eco*RI and Ad5 with *Sal*I, and then co-transfecting the digested DNA into 293 cells. Chinnadurai *et al.* found that recombination occurred between Ad2 *Eco*RI-A (map position 0 to 59) and Ad4 *Sal*I-A (map position 45 to 100). Chinnadurai *et al.*, Introduction, p. 623. The recombination seen by Chinnadurai *et al.* was between map positions 45 to 59.

The Ad plasmids (and methods) of the present claims differ from the DNA used by Chinnadurai *et al.* in their recombination experiments. Chinnadurai *et al.* do not teach a recombinant adenovirus devoid of sequences necessary for packaging and replication as recited in claims 22 and 26-27, nor do they teach the specific backbone plasmids recited in claims 28-34. Further, Chinnadurai et al. do not teach the use of plasmids at all; they only teach full-length infectious viral DNAs. Moreover, they do not teach a one-step transfection method. Therefore, Chinnadurai *et al.* alone does not anticipate the pending claims.

Aoki *et al.* do not teach the method of pending claims 22, 26-27. Page 225 of the reference describes the method used by Aoki *et al.* to generate their recombinant virus. Their method involved four steps: (1) in a cell-free reaction mixture equal moles of shuttle plasmid and adenoviral cosmid were recombined *in vitro* for 3 hours at 37°C along with Cre recombinase (except in the negative control), (2) the reaction mixture was inactivated at 70°C for 5 minutes, (3) DNA was purified using a plasmid purification kit, and (4) the DNA was transfected into 293 cells. In contrast, the method of claims 26-27 is a simple one-step process where a host cell is contacted with a shuttle plasmid and a backbone. No additional *ex vivo* enzymatic recombination, enzymatic inactivation, or DNA purification steps are required in the present method. Therefore, Aoki *et al.* alone does not anticipate the one-step method of claims 22, 26-27.

Further, Aoki *et al.* does not teach the backbone plasmids or shuttle plasmids as recited in the pending claims 28-34. The Aoki *et al.* plasmids contain loxP sequences, whereas the claimed plasmids do not. Therefore, Aoki *et al.* alone does not anticipate the pending claims.

Applicant asserts that even if Aoki *et al.* is combined with Chinnadurai *et al.*, these references do not teach the present invention. Neither Aoki *et al.* nor Chinnadurai *et al.* teach or suggest the backbone plasmids or shuttle plasmids as recited in the pending claims 28-34. Therefore, Chinnadurai *et al.* in combination with Aoki *et al.* do not teach the invention recited in claims 28-34.

Further, neither Aoki *et al.* nor Chinnadurai *et al.* teach or suggest the invention of claims 22, 26-27. When finding a claimed invention obvious, the references relied on must be

considered as a whole, and must also suggest the desirability of making the combination. *Lindemann Maschinefabrik GmbH v. American Hoist and Derrick Co.*, 221 USPQ 481, 488 (Fed. Cir. 1984). Furthermore, "[w]e do not 'pick and choose among the individual elements of assorted prior art references to recreate the claimed invention' but rather, we look for 'some teaching or suggestion in the references to support their use in the particular claimed combination.'" *Symbol Tech., Inc. v. Opticon, Inc.*, 19 USPQ2d 1241, 1246 (Fed. Cir. 1991) (quoting *Smithkline Diagnostics, Inc. v. Helena Lab. Corp.*, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988)); *see also, In re Sang Su Lee*, 61 U.S.P.Q.2d 1430-1436, 1433 (Fed. Cir. 2002).

The prior art does not contain some suggestion or incentive that would have motivated the skilled artisan to modify or to combine these references. The Introduction section of Aoki *et al.* discusses homologous recombination in mammalian helper cells between shuttle plasmid and an overlapping DNA of virus origin that has been rendered noninfectious. Aoki *et al.* specifically cites to Chinnadurai *et al.* regarding this homologous recombination method. Aoki *et al.* continues, however, by stating, "since homologous recombination is a rare event in mammalian cells, these procedures are often unpredictable, time-consuming, and difficult to control. To circumvent these problems of efficiency and contamination of wild-type adenovirus, we proposed using Cre-loxP recombination *in vitro*." Aoki at p. 224-225. Thus, one of ordinary skill in the art would not have had a reasonable expectation of success at the time the invention was made because there were so many known problems associated with homologous recombination methods.

Oftentimes one must guess at what one of ordinary skill in the art would do given the knowledge of the time. Here, we have the luxury of specifically knowing what one of skill in the art who was specifically aware of the teachings of Chinnadurai *et al.* and obviously the teachings of Aoki *et al.* (their own work). Aoki *et al.* were definitely skilled in the art and were aware of Chinnadurai *et al.*, and they chose to develop the Cre-loxP system, and not the system of the present invention. Thus, Aoki *et al.* taught away from using homologous recombination methods, and instead taught enzymatic recombination.

Further, Aoki *et al.* and Chinnadurai *et al.* cannot logically be combined. Chinnadurai *et al.* teaches a method of performing homologous recombination of infectious viral genomes, so as to generate viral particles. Aoki *et al.* teach a method of performing enzyme-mediated recombination to generate recombinant plasmids. One of skill in the art would not use Aoki *et al.*'s starting materials in the method of Chinnadurai *et al.* because one would not be able to generate the infectious viral genome that was the goal of Chinnadurai *et al.* Thus, the cited references do not contain the requisite suggestion or incentive that would have motivated the skilled artisan to modify a reference, or to combine references.

For these reasons, these references, even when taken in combination, do not meet the three requirements of *prima facie* obviousness. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

2. *Aoki et al. in view of Chinnadurai et al. and Krougliak et al.*

Claims 2, 3 and 6 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and Chinnadurai *et al.*, and further in view of Krougliak *et al.* (Human Gene Therapy, 6: 1575-1586 (1995)). These claims are cancelled, thereby rendering this rejection moot.

Insofar as Krougliak *et al.* may be applied to the pending claims, this rejection is hereby traversed. Krougliak *et al.* generated cell lines that could complement E1, E4 and protein IX defective adenovirus type 5 (Ad5) mutants. The plasmid system used by Krougliak *et al.* contained adenovirus sequences from the left ITR to the right ITR (*i.e.*, the full viral backbone), except for sequences encoding E1, E4 or protein IX. The intention of the deletions by Krougliak *et al.* was to provide for more space to accommodate larger inserts placed into the E1 region of the adenovirus vector and not to otherwise modify the backbone. Both Aoki *et al.* and Krougliak *et al.* devised strategies to make recombinant adenovirus only when the intact recombinant adenovirus genome that contained map units 0-1 and the left ITR was transfected into the cell. Recombination in this region was directly refuted by Aoki *et al.* and not attempted by Krougliak *et al.*, both of whom were extraordinarily skilled in the art.

Thus, none of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

3. *Aoki et al. in view of Chinnadurai et al., Krougliak et al. and Breakfield et al.*

Claims 7 and 8 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.*, Chinnadurai *et al.* and Krougliak *et al.*, and further in view of Breakfield *et al.* (U.S. 5,965,441). These claims are cancelled, thereby rendering this rejection moot.

Insofar as Breakfield *et al.* may be applied to the pending claims, this rejection is hereby traversed. Breakfield *et al.* does not remedy the shortcomings of Chinnadurai *et al.*, Aoki *et al.* and Krougliak *et al.* Breakfield *et al.* teach a hybrid vector system that incorporate elements of herpes virus and adeno-associated virus that is capable of expressing a gene product in eukaryotic cells. The Examiner admits that Breakfield *et al.* is deficient in that it does not teach an adenovirus vector. The Examiner states, however, that "one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate HSV Amplicon sequences into the backbone of Aoki *et al.* to expand the host range of gene expression to dividing cells."

The Examiner may not use hindsight to arrive at Applicant's invention, selecting aspects from four different references to attempt to piece together Applicant's invention. Even if one with skill in the art was motivated to combine these four references, when they are logically combined, one would have the Aoki *et al.* Ad vector containing a loxP sequence and the Breakfield *et al.* AAV/HSV hybrid sequences in the Krougliak *et al.* cell line (in a backbone containing the lefthand ITR). In contrast, the plasmids used in the present claimed cloning system do not contain loxP sequences or the lefthand ITR.

Thus, none of these references, either alone or taken in combination, teach the present claimed invention. Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

4. *Aoki et al. in view of Chinnadurai et al. and Chartier et al.*

Claim 12 was also rejected under 35 U.S.C. § 103(a) as being unpatentable over Aoki *et al.* and Chinnadurai *et al.*, and further in view of Chartier *et al.* (Journal of Virology, 70(7): 4805-4810 (1996)). This claim is cancelled, thereby rendering this rejection moot.

Therefore, Applicant respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

Conclusion

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612-373-6961) to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner of Patents, Washington, D.C. 20231, on this 18th day of November, 2002.

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